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ORIGINAL ARTICLE

Long-term outcome of kidney function in patients with ANCA-associated vasculitis

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ABSTRACT

Background. Kidney involvement is common in anti-neutrophil cytoplasm antibody–associated vasculitis (AAV) and the prognosis is determined by the severity of kidney damage. This study focused on long-term kidney outcomes, defining possible risk factors and comparing the performance of three different histological classifications to predict outcomes for patients with AAV.

Methods. The dataset included 848 patients with newly diagnosed AAV who participated in seven randomized controlled trials (RCTs) (1995–2012). Follow-up information was obtained from questionnaires sent to the principal investigators of the original RCTs.

Results. The cumulative incidence of end-stage kidney disease (ESKD) at 5 and 10 years was 17% and 22%, respectively. Patients who developed ESKD had reduced patient survival compared with those with preserved kidney function (hazard ratio 2.8, $P < .001$). Comparing patients with AAV and kidney involvement with a matched general population, patients with AAV had poor survival outcomes, even in early stages of chronic kidney disease. The main cause of death was infection followed by cardiovascular disease in patients developing ESKD and malignancy in those who did not. Some 34% of patients with initial need for dialysis recovered kidney function after treatment. Thirty-five out of 175 in need of kidney replacement therapy (KRT) during follow-up received a kidney transplant with good outcome; there was 86% patient survival at 10 years.
In the subcohort of 214 patients with available kidney biopsies, three scoring systems were tested: the Berden classification, the Renal Risk Score and the Mayo Clinic Score. The scores highlighted the importance of normal glomeruli and severe glomerulosclerosis on kidney survival ($P < .001$ and $P = .001$, respectively). The Renal Risk Score demonstrated a moderate prediction of kidney survival (area under the curve 0.79; standard error 0.03, 95% confidence interval 0.71–0.83).

Conclusions. Early diagnosis of AAV is extremely important. Even milder forms of kidney involvement have an impact on the prognosis. Patients in need of KRT had the lowest survival rates, but kidney transplantation has shown favorable outcomes for eligible AAV patients. The three histologic scoring systems were all identified as independent prognostic factors for kidney outcome.

Keywords: ANCA-associated vasculitis, end-stage kidney disease, kidney histology scores, prognosis, transplantation

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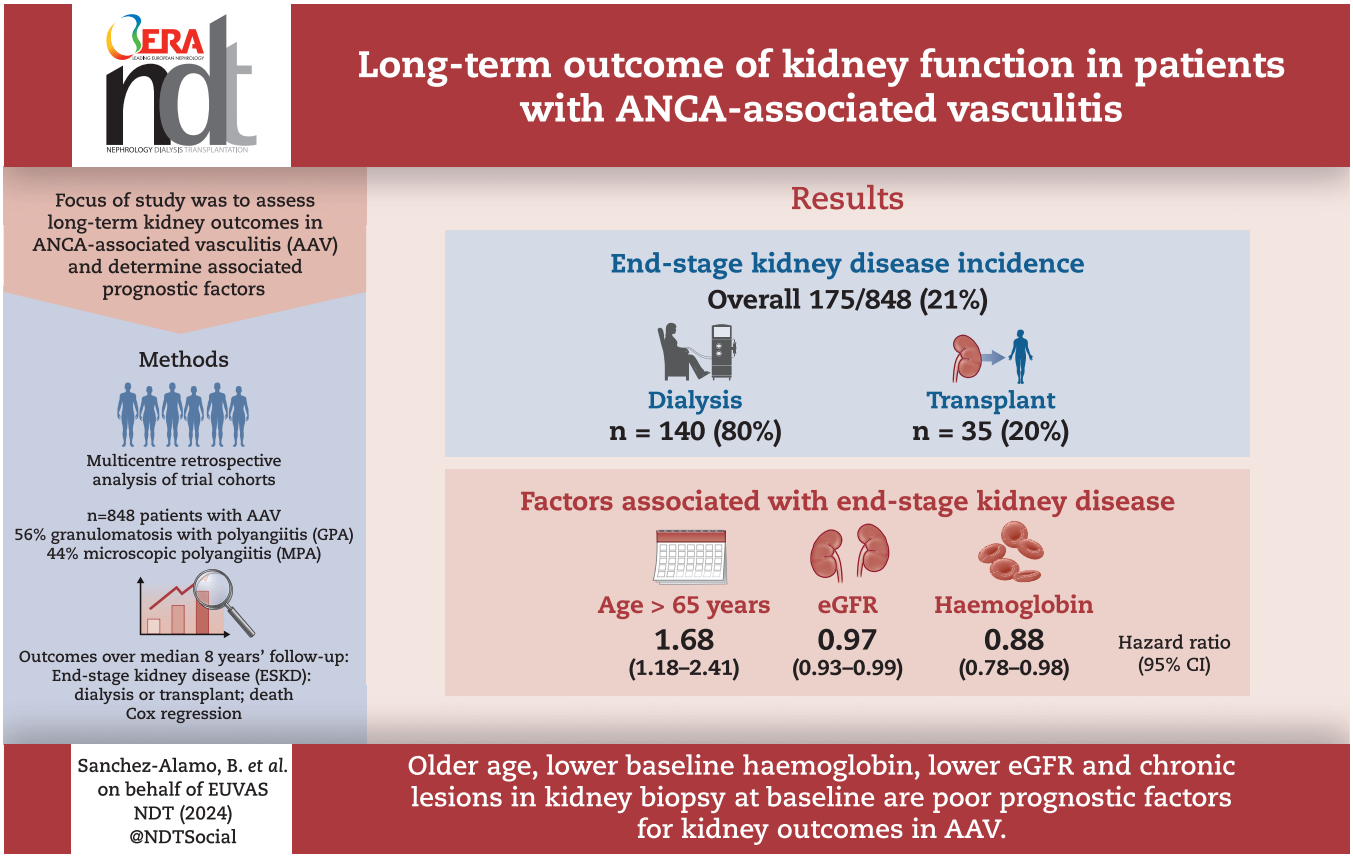
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Anti neutrophil cytoplasm antibody–associated vasculitis (AAV) is a heterogeneous disease that often involves the kidneys, and low glomerular filtration rate (GFR) is associated with bad outcome.
- The European Vasculitis Society has conducted several randomized clinical trials (RCTs) in AAV, but as the follow-up within the RCTs rarely extends beyond 2 years, we now have an extended, i.e. 10-year, follow-up of the first seven trials.

This study adds:

- The cumulative incidence of end-stage kidney disease (ESKD) is 22% after 10 years.
- Thirty-four percent of patients with ESKD and need for dialysis at time of diagnosis of AAV recovered kidney function during follow-up.
- Even a mild decrease in GFR is associated with worse patient survival.
- Kidney histology scores (the Berden classification, Renal Risk Score and the Mayo Clinic Chronicity Score) are useful tools for estimating prognosis.

Potential impact:

- It is extremely important to diagnose patients with AAV early as even a mild decrease in estimated GFR is associated with lower patient and kidney survival, even when no or few sclerotic changes in the kidney biopsy are detected.
- Histological classifications are useful to predict and stratify risk of poor outcomes in patients with AAV.
- In spite of ESKD at time of diagnosis there is a fair chance recovering kidney function with no subsequent need for dialysis.
- If ESKD kidney transplantation should be a first option if the patient has no contraindications.

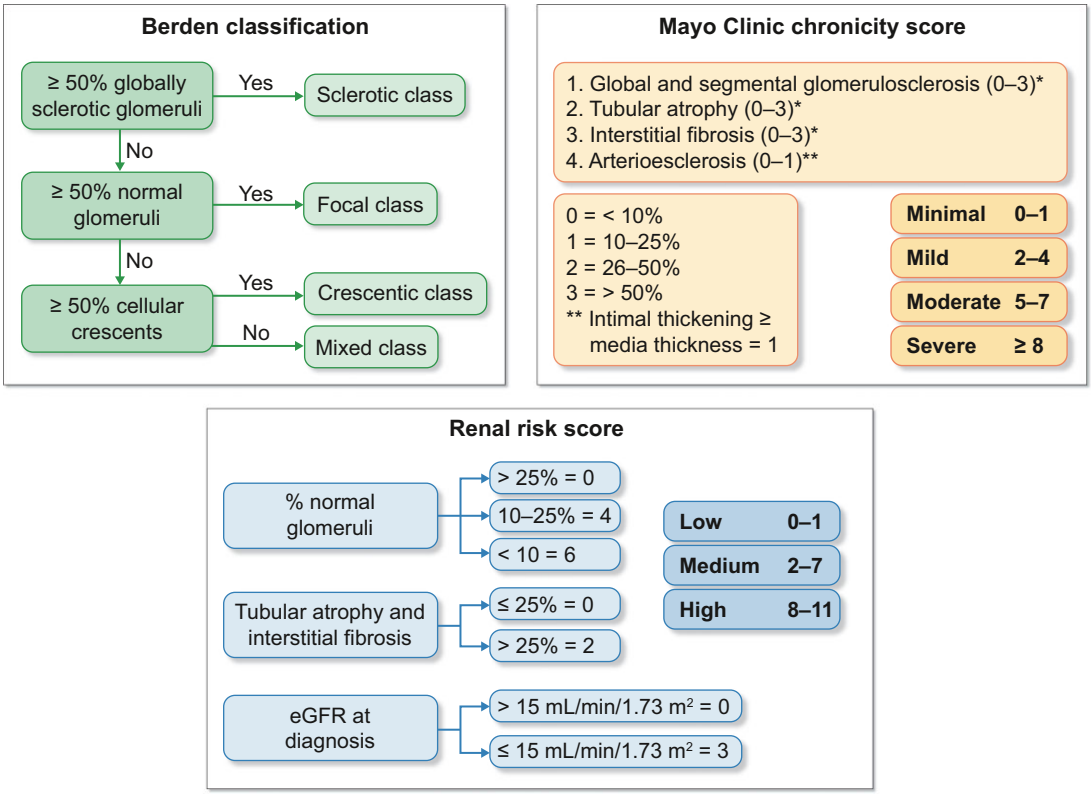


Figure 1: Histological classifications.

INTRODUCTION

Antineutrophil cytoplasm antibodies (ANCA)-associated vasculitis (AAV) is a group of autoimmune disorders that include microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA).

Kidney vasculitis is the most common severe manifestation of AAV, typically presenting with rapidly progressive glomerulonephritis (GN), hematuria and glomerular proteinuria [1]. However, many patients with AAV display a "silent" kidney involvement with isolated microscopic haematuria and cylindruria in the early phases [2].

AAV represents almost 20% of biopsy-proven GN [3], and it is a frequent finding in kidney biopsies from elderly patients. Among kidney biopsies performed on patients between 65 and 80 years old, 14.3% correspond to vasculitis, and in patients ≥80 years, 19% of the biopsies show vasculitis [4–6]. AAV-GN commonly presents as a pauci-immune necrotizing crescentic GN [7]. Although pauci-immune, small amounts of IgG or C3 may be seen in the kidney biopsy, and if present, associated with more severe disease [2].

The kidney prognosis of AAV differs greatly but kidney impairment is a major predictor of poor kidney and patient survival. Furthermore, the histological findings on kidney biopsy also have a strong prognostic value [8]. Various histological classifications of AAV have been developed as attempts to evaluate the risk of progressing to end-stage kidney disease (ESKD) (Fig. 1); there are the International Pathology Classification or Berden classification [9], as well as the one from Brix *et al.*, in the form of the Renal Risk Score (RRS) [10, 11], and the Mayo Clinic Chronicity Score (MCCS) [12–14].

During the last 25 years, the European Vasculitis Society (EUVAS) has run several prospective randomized clinical trials as an attempt to improve outcome for patients with a broad spectrum of AAV. Ten years ago, EUVAS presented a follow-up study including patients from four randomized clinical trials (RCTs), Non-renal wegener's granulomatosis treated alternatively with methotrexate (NORAM), CYC versus AZA for early remission phase of vasculitis trial (CYCAZAREM), Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis (CYCLOPS) and Plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis (MEPEX) [15]. The current study collected information from the patients of these four studies in combination with information from patients from later RCTs: International Mycophenolate mofetil protocol to reduce outbreaks of vasculitides (IMPROVE), Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis (MYCYC) and Rituximab versus cyclophosphamide in ANCA-associated vasculitis (RITUXVAS).

The aim of this study was to estimate the frequency of ESKD and define possible risk factors for ESKD among patients with AAV who have participated in EUVAS's prospective RCTs, and furthermore, to compare the performance of three different histological classifications to predict outcomes for patients with AAV.

MATERIALS AND METHODS

Study population

The study population consisted of 848 patients with an AAV who participated in EUVAS RCTs during 1995–2012 (NORAM,

CYCAZAREM, CYCLOPS, MEPEX, IMPROVE, RITUXVAS, and MYCYC), all patients with newly diagnosed AAV and who fulfilled the American College of Rheumatology criteria (1990) and Chapel Hill consensus definition (1994) for GPA and MPA [16, 17].

Baseline evaluation

Data recorded at trial entry included ANCA type [proteinase 3 (PR3) and myeloperoxidase (MPO)], full blood count and serum creatinine. Disease activity was assessed by the Birmingham Vasculitis Score (BVAS) [18]. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [19].

Follow-up data

Information on follow-up was obtained from questionnaires to the principal investigators of the RCTs respectively, and retrieved from 70% out of the total cohort of 848 patients, described in detail in our previous report [20]. The present study was performed in accordance with the principles in 1964 Declaration of Helsinki and amendments and ethical approval obtained by national and local ethics committees in accordance with national legislation.

Kidney biopsies and histopathological scores

Three different scores were used to test prognosis for the kidney outcome: the Borden Classification [9], the RRS [10] and the MCCS [12, 21]. Biopsies with a minimum of five glomeruli were included in the present investigation. It has been demonstrated previously that >3 glomeruli is adequate for histological classification when compared with the evaluation of patients with ≥10 glomeruli [8].

Kidney biopsies were available for analyses on a subcohort of 214 patients. Mean number of glomeruli per sample was 14.3 ± 8.1.

All biopsies were scored independently by two pathologists, who were blinded to patient data, from a group of five pathologists, according to a previously standardized protocol; discrepancies were resolved during consensus meetings.

Endpoints

The kidney endpoint was defined as ESKD (permanent dialysis dependency during follow-up or kidney transplantation) and the combined endpoint as death or ESKD.

Kidney survival was expressed as time from entry into the respective RCT, to the time of ESKD, and patient survival as time to death.

Statistical analysis

Categorical variables were presented as number (percentage) and continuous variables as mean (standard deviation) if normally distributed as determined by the Shapiro–Wilk test or as median [interquartile range (IQR)] if non-normal. For comparisons of categorical variables between groups, the Pearson's chi-square test was used if the number of elements in each cell was ≥5; the Fisher's exact test was performed. To compare two categories of continuous variables between groups, we employed an unpaired Student's *t*-test for independent samples when the distributions were consistent with normality. Alternatively, if the normality assumption was violated, we utilized the Mann–Whitney U-test.

For the comparison of more than two categories of continuous variables between groups, we employed an analysis of variance test when the distributions were consistent with normality. If the assumption of normality was not met, the Kruskal–Wallis test was applied. The Bonferroni correction was applied. The Kaplan–Meier method was used to assess the cumulative incidence of ESKD, time to death and cumulative incidence of combined endpoints. Cox proportional hazards regression models were employed to determine predictive factors for the outcomes.

A multivariate Cox regression model was performed to examine the factors associated with the outcomes. The first Cox regression model included all the patients of our cohort and the following covariates were included: age, sex, clinical diagnosis (MPA or GPA), baseline eGFR (mL/min/1.73 m^2) and baseline hemoglobin levels (g/dL).

A second multivariate Cox regression model when restricted to patients with kidney biopsy with following covariates included: age, baseline eGFR (mL/min/1.73 m^2), percentage of normal glomeruli and degree of glomerulosclerosis according to the classification of MCCS (<10%, 10%–25%, 26%–50% and >50%).

We used Ederer II method to estimate the relative survival rates for the study cohorts. Relative survival is the difference between the total (all-cause) mortality rate among the patients and the expected mortality rate of a comparable group from the general population, matched to the patients with respect to the main factors affecting patient survival (e.g. age, sex and calendar year). Data on the expected survival for the general population were obtained from nationwide population life tables stratified by age, sex and calendar time hosted by the Human Mortality Database (HMD) [22]. The life tables from HMD contain general population survival probabilities (conditional probabilities of surviving 1 year) stratified by those variables that uniquely determine the records and on which it is assumed that expected survival depends, in this case calendar year, age, sex and country.

SPSS Statistics version 28 (IBM, Armonk, NY, USA) and STATA 14 were used for data analysis, while GraphPad Prism (version 9) was used to design the figures.

RESULTS

Patients' baseline characteristics

A total 848 patients were enrolled, and the median follow-up time of the entire cohort was 7.96 years (IQR 2.95–13.64). Some 478 (56.40%) patients had GPA and 370 (43.6%) MPA. Mean age at diagnosis was 58 ± 14.2 years. Renal involvement was detected in 644 (76%) patients at diagnosis, with a median eGFR of 42.1 (IQR 16.2–88.6) mL/min/1.73 m^2 (clinical characteristics presented in Table 1). At baseline, 199 patients had an eGFR <15 mL/min/1.73 m^2, 144 had an eGFR 15–30 mL/min/1.73 m^2 and another 183 had an eGFR 30–60 mL/min/1.73 m^2. A total of 107 patients needed dialysis at initial AAV presentation.

Kidney survival

The cumulative incidence of ESKD was 11.3%, 16.9%, 22.5% and 26.8% at 1, 5, 10 and 15 years, respectively (Supplementary data, Fig. S2).

At follow-up, 175 patients (20.6%) were recorded with ESKD and required kidney replacement therapy (KRT), out of which, 35 patients received a kidney transplant and another 140 dialysis. Some 108 (62%) of those with ESKD had MPA, 67 (38%) GPA and 86 (49.1%) had MPO-ANCA.

Patients with ESKD had a median baseline eGFR at entry of 13.2 (IQR 7.3–26) mL/min/1.73 m^2, were older (62.3 ± 13.4 vs 56.9 ± 14.1 years; $P < .001$), had a significantly higher baseline creatinine at randomization 482 (IQR 294–732) vs 143 (IQR 89–281) μmol/L; $P < .001$), lower baseline hemoglobin levels (9.2 ± 1.8

Table 1: Baseline characteristics at entry into RCTs for the entire cohort with respect to renal kidney outcome.

		Entire cohort, N = 848	No ESKD, N = 673 (79.4%)	ESKD, N = 175 (20.6%)	P-value
Male sex (*n*, %)		474 (55.9)	374 (55.6)	100 (57.1)	0.7
Age (years)		58 ± 14.2	56.9 ± 14.1	62.3 ± 13.4	**<.001**
Diagnosis (*n*, %)	GPA	478 (56.4)	411 (61.1)	67 (38.3)	**<.001**
	MPA	370 (43.6)	262 (38.9)	108 (61.7)	
ANCA (*n*, %)	MPO	326 (40.5)	240 (37.7)	86 (49.1)	**.002**
	PR3	478 (59.5)	396 (62.3)	82 (48.8)	
BVAS		18 ± 8.3	17.8 ± 8.5	18.8 ± 7.5	.1
RCTs (*n*, %)	CYCAZAREM	155 (18.3)	135 (20.1)	20 (11.4)	**<.001**
	CYCLOPS	143 (16.9)	114 (16.9)	29 (16.6)	
	IMPROVE	167 (19.7)	144 (21.4)	23 (13.1)	
	MEPEX	137 (16.2)	62 (9.2)	75 (42.9)	
	MYCYC	116 (13.7)	101 (15)	15 (8.6)	
	NORAM	94 (11.1)	90 (13.4)	4 (2.3)	
	RITUXVAS	36 (4.2)	27 (4)	9 (5.1)	
Creatinine (μmol/L)[a]		176 (97–388.5)	143 (89–281)	482 (294–732)	**<.001**
eGFR (mL/min/1.73 m^2)[a]		42.1 (16.2–88.6)	53.4 (24.8–94.1)	13.2 (7.3–26.04)	**<.001**
eGFR (mL/min/1.73 m^2) (*n*, %)	>90	203 (24)	195 (29)	8 (4.6)	**<.001**
	60–90	118 (13.9)	113 (16.8)	5 (2.9)	
	30–60	183 (21.6)	161 (23.9)	22 (12.6)	
	15–30	144 (17)	104 (15.5)	40 (23)	
	<15	199 (23.5)	100 (14.9)	99 (56.9)	
Hemoglobin (g/dL)		10.1 ± 2	10.3 ± 2	9.1 ± 1.8	**<.001**
WBC (10^9/L)		11.8 ± 4.7	11.8 ± 4.5	11.9 ± 5.3	.9
Platelet (10^9/L)		397.4 ± 168.8	405.6 ± 164.3	365.8 ± 182.1	**.006**

Values for continuous variables are expressed as mean ± standard deviation or [a]median (IQR), and values for categorical variables as percentage. The GFR was estimated using the CKD-EPI equation. Bold values denotes statistically significant values.
WBC: white blood cells.

Table 2: Baseline characteristics with respect to KRT at follow-up.

		No ESKD, n = 673 (79.4%)	Kidney transplant, n = 35 (4.1%)	Dialysis, n = 140 (16.5%)	P-value
Male sex (*n*, %)		374 (55.6)	23 (65.7)	77 (55)	.5
Age (years)		56.9 ± 14.1	47.8 ± 12.8	65.9 ± 10.9	**<.001**
Diagnosis (*n*, %)	GPA	411 (61.1)	16 (45.7)	51 (36.4)	**<.001**
	MPA	262 (38.9)	19 (54.3)	89 (63.6)	
ANCA (*n*, %)	MPO	240 (37.7)	16 (50)	70 (51.5)	**.007**
	PR3	396 (62.3)	16 (50)	66 (48.5)	
Countries (*n*, %)	North	310 (46.1)	15 (42.9)	75 (53.6)	.1
	South-West	363 (53.9)	20 (57.1)	65 (46.4)	
Randomization period (year)	1995–1999	299 (44.4)	21 (60)	74 (52.9)	**.04**
	>2000	374 (55.6)	14 (40)	66 (47.1)	
Creatinine (μmol/L)[a]		143 (89–281)	335 (218–517)	539 (315.5–755)	**<.001**
eGFR (mL/min/1.73 m^2)[a]		53.4 (24.8–94.1)	23 (13.6–32.9)	11.3 (6.9–21)	**<.001**
eGFR (mL/min/1.73 m^2) (*n*, %)	>90	195 (29)	4 (11.4)	4 (2.9)	**<.001**
	60–90	113 (16.8)	0 (0)	5 (3.6)	
	30–60	161 (23.9)	8 (22.9)	14 (10.1)	
	15–30	104 (15.5)	11 (31.4)	29 (20.9)	
	<15	100 (14.9)	12 (34.3)	87 (62.6)	
Hemoglobin (g/dL)		10.3 ± 2	9.5 ± 1.8	9 ± 1.8	**<.001**
WBC (10^9/L)		11.8 ± 4.5	10.4 ± 3.4	12.2 ± 5.6	.1
Platelet (10^9/L)		405.6 ± 164.3	372.1 ± 140.8	364.2 ± 191.6	**.02**
Follow-up time (years)		8.3 (3.7–14.1)	12.8 (9–18.2)	3.8 (0.7–8.8)	**<.001**

Values for continuous variables are expressed as mean ± standard deviation or [a]median (IQR), and values for categorical variables as percentage. The GFR was estimated using the CKD-EPI equation. Bold values denotes statistically significant values.
WBC: white blood cells.

vs 10.3±2 g/dL; $P < .001$) and lower platelet counts (365.8 ± 182.1 vs 405.6 ± 164.3 × 10^9/L; $P = 0.006$) (Table 1).

At follow-up, 37 out of the 107 with ESKD at entry to the RCTs recovered kidney function later and 26 remained out of KRT during follow-up, but 11 patients needed subsequent dialysis.

Patients who received kidney transplants were significantly younger (47.8 ± 12.8 vs 65.9 ± 10.9 years; $P < .001$), had a higher median baseline eGFR [23 (IQR 13.6–32.9) vs 11.3 (IQR 6.9–21) mL/min/1.73 m^2], higher baseline hemoglobin levels (9.5 ± 1.8 vs 9 ± 1.8 g/dL; $P < .001$) and a slightly higher platelet count

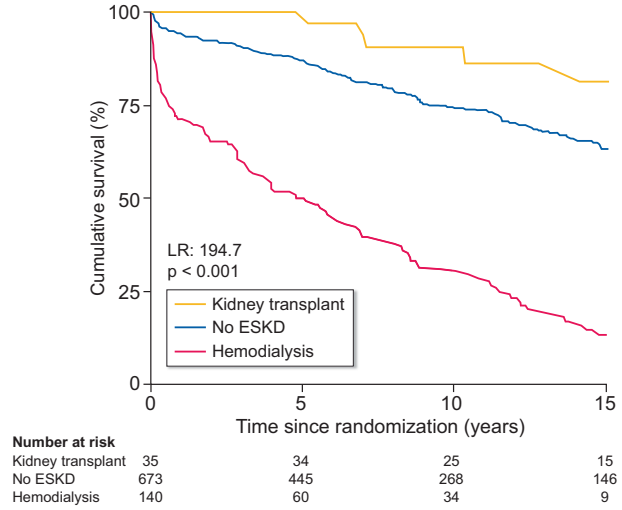


Figure 2: Patient survival Kaplan–Meier curves grouped by kidney transplant, ESKD or no ESKD.

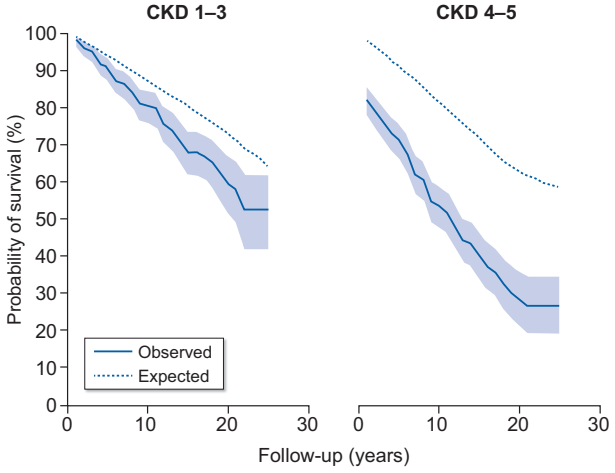


Figure 3: Patients' survival according to chronic kidney disease (CKD) stage inclusion and in a matched cohort by age, sex and country (Ederer II method).

(372.1 ± 140.8 vs 364.2 ± 191.6; $P = .02$), compared with patients on dialysis (Table 2).

Patient and kidney outcomes

Patients who developed ESKD had increased mortality [Log-rank (LR) 97.2; $P < .001$] [hazard ratio (HR) 2.8; $P < .001$] (Supplementary data, Fig. S2). Of the 175 patients with ESKD, 118 died (67.4%) and mortality was higher in the group of patients on dialysis [$n = 110$ (78.6%)], compared with the group of kidney transplant recipients [$n = 8$ (22.8%)]. GPA patients with ESKD had a better prognosis compared with those with MPA (HR 5.4; $P = .02$).

Among those who developed ESKD, the most frequent causes of death were infections (29.7%), cardiovascular disease (16.9%) and malignancies (5.9%). In contrast, for individuals who did not develop ESKD, the primary causes of death were infections (23%), followed by malignancies (16.6%) and cardiovascular disease (12.3%).

The survival rates for hemodialysis patients were lower at each time period. Specifically, the rates at 1, 5, 10 and 15 years were 71.4%, 49.3%, 30.6% and 13.2%, respectively.

Kidney recipients had a better patient survival compared with patients receiving dialysis (LR 194.7; $P < .001$) (Fig. 2). Patient survival rates after the first kidney transplantation at 1, 5, 10 and 15 years, were 100%, 97.1%, 86.5% and 81.4%, respectively.

A total of 362 (42.7%) patients in the cohort reached the combined endpoint (defined as death or ESKD). The cumulative incidence of the combined endpoint was 15.6%, 25.4%, 40% and 51.7% at 1, 5, 10 and 15 years, respectively.

When compared with a matched general population (matched by age, sex and country), AAV patients with kidney impairment displayed a worse prognosis. Even patients in the initial stages of chronic kidney disease [1–3] had worse prognosis than the general population (Fig. 3).

Kidney histology

Some 214 kidney biopsies were obtained from four RCTs: 87 from the MEPEX (40.7%), 83 from the CYCAZAREM (38.8%), 13 from the CYCLOPS (6.1%) and 31 from the RITUXVAS (14.5%). Sixty-seven (31.3%) developed ESKD, 119 of them (55.6%) reached the combined endpoint and 103 out of 214 (48.1%) patients died.

The percentage of normal glomeruli was higher in the group of patients not reaching ESKD and they had lower amounts of glomerulosclerosis, interstitial fibrosis and tubular atrophy (IFTA) as well as cellular crescents (Supplementary data, Table S1).

According to the Berden classification, biopsies from patients with AAV were categorized into focal ($n = 51$, 23.8%), crescentic ($n = 97$, 45.3%), mixed ($n = 39$, 18.2%) and sclerotic ($n = 27$, 12.6%) (Supplementary data, Fig. S2 and Table S2). As per the Kaplan–Meier curves, sclerotic class had the worst survival for the kidney endpoint (LR 23.9; $P < .001$) (Fig. 4). Reproducible findings were observed for the combined endpoint (Supplementary data, Fig. S4). Kidney survival rate at 15 years was 37% in the sclerotic class, 48% in the crescentic class, 58% in the mixed class and 89% in the focal class (Fig. 4A, Supplementary data, Table S3).

Regarding the RRS classification, 56 (26.2%), 79 (36.9%) and 79 (36.9%) biopsies were classified as low, moderate and high risk of kidney failure, respectively. Patients at higher risk according to the RRS were older and had lower eGFR values at baseline (Supplementary data, Table S4). In the high-risk group more patients reached ESKD compared with the moderate- and low-risk patients [47 (59.5%) vs 18 (22.8%) vs 2 (3.6%); $P < .001$]. Similar findings were replicated for the combined endpoint [64 (81%) vs 40 (50.6%) vs 15 (26.8%); $P < .001$]. Kidney survival rates for the low-, moderate- and high-risk classes at 15 years were 94%, 61% and 31%, respectively (Fig. 4B, Supplementary data, Table S4).

Following the MCCS, chronic damage was minimal in 23 (10.7%), mild in 72 (33.6%), moderate in 72 (33.6%) and severe in 47 (22%) biopsies. Patients in the severe chronic changes group were older with less baseline kidney function (Supplementary data, Table S5), experiencing higher mortality rates and ESKD occurrence. Kidney survival at 15 years for the minimal, mild, moderate and severe chronicity groups were 91%, 70%, 50%, and 37%, respectively (LR 18.2; $P < .001$) (Fig. 4C, Supplementary data, Table S5).

Kidney and patient survival

A multivariate Cox regression model including all patients revealed that age >65 years (HR 1.68; 95% CI 1.18–2.41; $P = .005$), lower baseline eGFR (HR 0.97; 95% CI 1.0009–1.0018; $P < .001$) and lower baseline hemoglobin levels (HR 0.88; 95% CI 0.78–0.98; $P = .02$) were negative prognostic factors (Table 3).

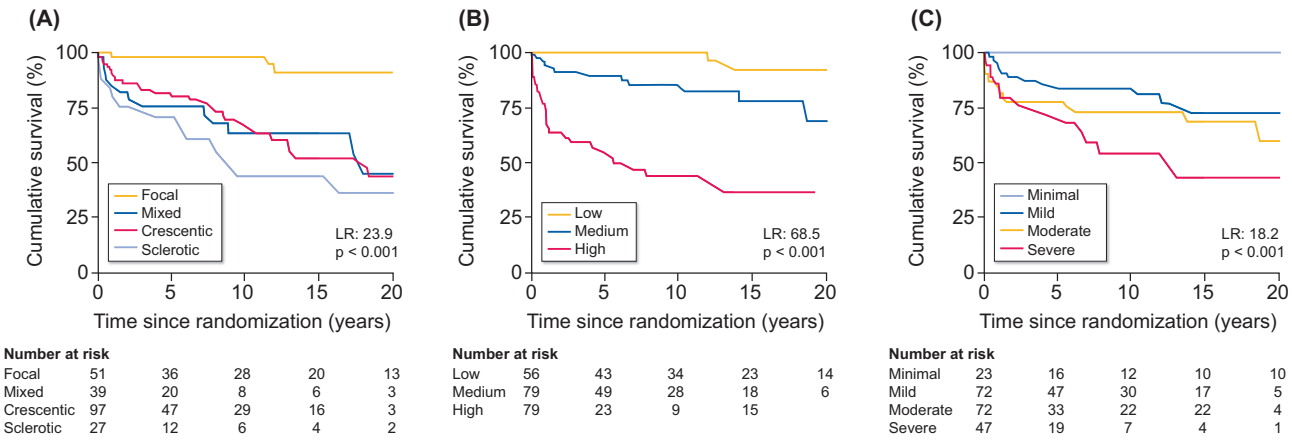


Figure 4: Kaplan–Meier curves for the kidney endpoint according to three histological classifications: Berden (**A**), RRS (**B**) and MCCS (**C**).

Table 3: Results from the multivariable Cox regression analysis (univariate and multivariate analysis) for the kidney endpoint.

	Univariate			Multivariate		
Variables	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Kidney endpoint—all the patients						
MPA	2.02	1.44–2.86	<.001	1.14	0.80–1.64	.5
Male	1.34	0.94–1.91	.1	1.28	0.89–1.84	.2
eGFR (mL/min/1.73 m^2)	0.97	0.96–0.97	<.001	**0.97**	0.93–0.99	**<.001**
Age >65 years old	2.49	1.76–3.53	<.001	**1.68**	1.18–2.41	**.005**
Hemoglobin (g/dL)	0.75	0.68–0.83	<.001	**0.88**	0.78–0.98	**.02**
Kidney endpoint—patients with kidney biopsy						
Normal glomeruli (%)	0.94	0.92–0.96	<.001	**0.96**	0.93–0.98	**.002**
Mild glomeruloesclerosis	1.55	0.68–3.53	.3	2.20	0.94–5.14	.07
Moderate glomeruloesclerosis	3.52	1.54–8.05	.003	1.93	0.84–4.42	.1
Severe glomeruloesclerosis	3.87	1.73–8.64	.001	**2.87**	1.26–6.57	**.01**
Age >65 years old	2.37	1.67–3.37	<.001	1.41	0.75–2.65	.3
eGFR (mL/min/1.73 m^2)	0.97	0.96–0.97	<.001	**0.96**	0.93–0.99	**.005**

Glomeruloesclerosis was classified according to the MCCS into four categories: minimal (<10%), mild (10–25%), moderate (26–50%) and severe (>50%). Bold values denotes statistically significant values.

When the multivariate Cox regression model was restricted to the subcohort of patients with kidney biopsies, the percentage of normal glomeruli (HR 0.96; 95% CI 0.93- 0.98; $P = .002$), severe degree of glomerulosclerosis (HR 2.87; 95% CI 1.26–6.57; $P = .01$) and lower baseline eGFR (HR 0.96; 95% CI 0.93–0.99; $P = .005$) were prognostic factors for the renal endpoint (Table 3).

Regarding combined endpoint, a multivariate Cox regression adjusted for age and sex revealed that the different histological classifications significantly correlated with both outcomes. The patients at higher risk for the kidney endpoint were those with severe chronic damage according to the MCCS classification, those in the sclerotic class according to the Berden classification and the kidney biopsies classified as high risk according to the RRS (Fig. 4).

Results for the multivariate Cox regression for the combined endpoint are compiled in Supplementary data, Table S6.

Performance of the different histological classifications

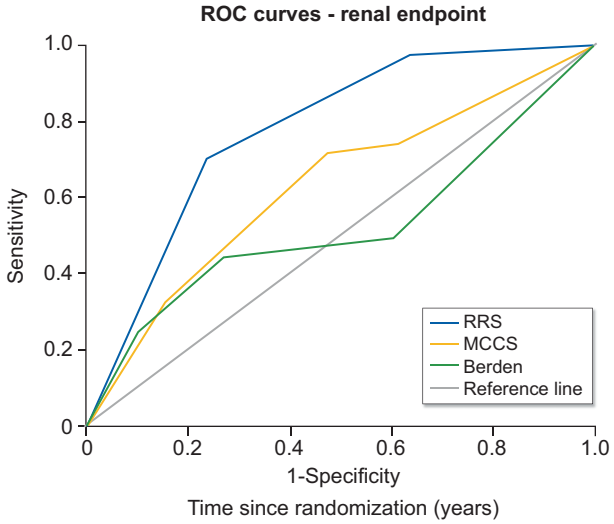
To test the performance of the different histological classifications, the areas under the curve (AUC) from the respective receiver operating characteristic (ROC) curves were compared. The results of the RRS [AUC 0.79; Standard deviation (SD) 0.03; 95% CI 0.71–0.83] and MCCS (AUC 0.63; SE 0.04; 95% CI 0.55–0.70) were significant for AUC in predicting the kidney endpoint, while the Berden classification had a modest and non-significant AUC (AUC 0.52; SE 0.05; 95% CI 0.43–0.60) (Fig. 5).

For the combined endpoint, the ROC curve from the RRS showed the best performance, exhibiting the highest AUC (AUC 0.74; SE 0.03; 95% CI 0.67–0.79). The MCCS followed next best performance (AUC 0.65; SE 0.04; 95% CI 0.58–0.72) and the Berden classification showed the lowest performance (AUC 0.51; SE 0.5; 95% CI 0.43–0.58).

DISCUSSION

Kidney involvement is a common and severe complication of AAV and has a considerable impact on patient survival [23]. To our knowledge, our study is the largest with the longest follow-up of patients with AAV and kidney involvement. We found a renal survival of 78% at 10 years for the whole cohort.

We have demonstrated that even milder forms of kidney involvement have an impact on prognosis. A previous study including patients with kidney involvement ($n = 212$) versus non-renal ($n = 61$), demonstrated a superior survival in the non-kidney involvement group. However, when comparing survival



	AUC	SE	95% CI	P-value
RRS	0.79	0.03	0.71–0.83	< 0.001
MCCS	0.63	0.04	0.55–0.70	< 0.001
Berden	0.52	0.05	0.43–0.60	0.96

Figure 5: ROC curves for the kidney endpoint according to the histological classifications.

of patients with mild to moderate kidney impairment not in need of KRT, it was found by de Joode *et al.* that it was not statistically significant different from patients in the nonrenal group [24].

Renal prognosis in patients with AAV is still unfavorable and up to 28% of the newly diagnosed patients will reach ESKD [25]. In a study based on the European registry, including 2511 patients with vasculitis who started KRT between 1993 and 2012, the incidence of dialysis-dependent vasculitis was estimated as 1.5 people per million inhabitants [26]. In our study the cumulative incidence of ESKD was 26.8% at 15 years. The factors that affect kidney survival are similar to those that influence mortality—a low eGFR at baseline, as well as the need for dialysis at presentation, predicted ESKD [27, 28].

In our study, the median baseline eGFR of recruited patients was 42.1 mL/min/1.73 m^2 (IQR 16.2–88.59), but it was lower in those patients who reached ESKD during follow-up [13.2 mL/min/1.73 m^2 (IQR 7.3–26.04)]. Although 37 out of 107 of those requiring KRT at entry regained kidney function, 26 out of the 37 returned to KRT during subsequent long-term follow-up. Once kidney damage occurs, if not treated properly, it will trigger fibrosis, which clinically translates as a decrease in eGFR. Histologically, the number of intact glomeruli and histopathological features of chronic damage (the percentage of glomerulosclerosis and the degree of IFTA) are important predictive factors for ESKD [11, 29]. Within our analysis, the percentage of normal glomeruli was higher in the group of patients that did not develop ESKD. IFTA has been demonstrated in the univariate analysis to be a risk factor for renal outcome. However, we excluded this parameter from the multivariate model because interobserver agreement was low [30]. These findings highlight the need to diagnose patients with AAV in the early phases of the disease when there is less chronic damage and the importance of early initiation of adequate immunosuppressive therapy.

The results in this cohort indicate that the kidney prognosis is better in patients with GPA than for those with MPA. Perhaps due to MPO-AAV presenting with more sclerotic and mixed classes than PR3-AAV, whereas in PR3-AAV patients, the focal class was found in a higher percentage. These results are in line with previously presented data [28]. In addition, other studies have also found a lower proportion of normal glomeruli and higher proportions of fibrous crescents, glomerular sclerosis and interstitial fibrosis in MPO-AAV than in PR3-AAV [31, 32].

The survival of patients with kidney transplant in our cohort is comparable, and even in some cases higher, than international reports [33]. This could be explained by their younger age. Their immune suppressive treatment exposure over time might impact transplant and survival outcome [34].

However, kidney transplantation in patients with AAV appears to have a favorable graft and patient survival compared with other ESKD patients with other diagnoses. Shen *et al.*, reported that patient and graft outcomes in kidney transplant recipients with GPA were superior to those who received kidney transplants due to other causes [35]. Hruskova *et al.* demonstrated that patient survival after kidney transplantation in patients with AAV was not inferior to that in a matched control, and was superior to both the matched control group of patients with diabetes mellitus and the non-diabetic control group. However, graft survival in the AAV group was superior in comparison with all control groups [26].

It should be observed that patients with AAV should have at least 1 year of complete remission before receiving a kidney transplant [36]. A review of outcome of kidney transplantation in patients with AAV revealed a low relapse rate after transplantation [37]. Unfortunately, we were not able to analyse the risk for kidney relapse post-transplantation in our present material. Nevertheless, the cumulative (kidney and patient) survival rate was high amongst the transplanted patients, 86% at 10 years, in our cohort, indicating that there was not a clinically overt risk for frequent or severe relapses.

Kidney biopsy is an established method routinely used to establish diagnosis and predict prognosis in kidney vasculitis. When histological factors are taken into account to predict ESKD, the percentage of normal glomeruli and the severity of glomerulosclerosis have been found to be important [11, 29]. The percentage

of normal glomeruli was higher in the group of patients that did not develop ESKD. This finding emphasizes the need to diagnose patients with AAV in the early phases of the disease when there is less chronic damage. In our study, IFTA has been demonstrated in the univariate analysis to be a risk factor for the kidney outcome. However, we excluded the parameter from the multivariate model because interobserver agreement was low [30]. These results may not be generalizable to all AAV patients, especially with extrarenal manifestations and milder symptoms.

We have shown how different ANCA-GN classification models predict kidney and patient survival. Our results also validate the long-term predictions of the RRS, MCCS and the Berden prediction systems. In relation to the RRS, the classification of low, medium and high risk perfectly correlated with both kidney, and the combined endpoint. MCCS has demonstrated its validity as a prognostic tool for assessing outcomes in AAV-GN. Higher degrees of chronicity grades were associated with an increased risk for kidney and combined outcomes. According to the Berden classification, patients with the focal class had the best renal outcome and the worst kidney outcome was associated with the sclerotic class, but we have found no significant difference in the outcomes between the mixed and crescentic classes as has been previously reported by other authors [29, 38, 39].

The results of the ROC analyses indicate that the RRS classification was the most accurate prognostic model, but is the only one that incorporates eGFR, which has repeatedly been shown to be a strong predictor of kidney and patient outcome [20, 27]. Therefore, it is not surprising that this classification exhibited a higher accuracy. It should be noted that the Berden classification solely assesses the glomerular compartment, while the RRS and the MCCS include tubulointerstitial features for prognosis prediction in AAV-GN [12]. This additional consideration of tubulointerstitial features may help to explain the aforementioned findings. Additional studies are warranted to establish the usefulness of these classifications to guide therapeutical practice at various degrees of kidney involvement.

The major strength of this study is the large population with defined diagnoses and extended follow-up time. Extended follow-up in RCTs is necessary to establish the long-term benefit of treatments and to characterize late treatment-related side effects. Clinically important findings may emerge several years after completion of treatment and often after discontinuation of formal follow-up [40].

Critics may be concerned about the somewhat dated induction treatment used for the majority of patients, i.e. cyclophosphamide, and not an anti-CD20 monoclonal antibody such as rituximab. However, the cohort included many patients with advanced kidney disease where cyclophosphamide still remains an alternative [36]. In addition, recommendations for glucocorticoid dosing aiming for a reduction in the total amount and usage of plasma exchange has changed since the publications of the protocols from our RCTs. Nevertheless, results obtained from our study are valuable when comparing newer treatments observed by a long-term follow-up [41, 42].

A limitation of this study is that the patients were part of different RCTs and therefore concerns might arise about the external validity of the study. In the study conducted by Pagnoux *et al.*, when RCT patients were compared with cohort patients, a number of differences were found. RCTs patients were older at diagnosis than the cohort patients, and had more severe forms of the disease (higher BVAS score, and more frequent kidney disease). Mortality and relapse rates were higher for patients with GPA in RCTs, but similar for patients with MPA [43]. Patients with less active forms of disease or extremely life-threatening disease may not be included in a RCT. Some may have died quickly or had severe disability and therefore not been referred to tertiary centers, where patients are entered in cohorts, thereby resulting in bias when analyzing patients' outcomes due to an underestimation of the rate of adverse events [44]. However, our cohort comprised a large proportion of patients with AAV and even patients with severe kidney renal involvement and even dialysis dependency. A limitation of our study is the lack of information regarding data on comorbidities and vascular damage index (VDI) at follow-up.

Some patients with AAV, particularly those with MPA, have a "silent" kidney involvement only revealed by a microscopic hematuria, and thus may go undiagnosed for a considerable time. On the contrary, patients with a rapid decline in kidney function leading to ESKD, have less chance of regaining kidney function. As has been shown previously, it is important to diagnose patients with AAV early, when the kidney tissue and function are preserved. It therefore seems important to highlight the risk of ESKD among patients with AAV and to try to identify these patients at an early stage and have a kidney biopsy performed.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

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CONFLICT OF INTEREST STATEMENT

None declared.

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